

Stomach interference in ^{82}Rb -PET myocardial perfusion imaging

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Background. ^{82}Rb -positron-emission-tomography (PET) is prone to some of the same imaging artifacts as single-photon-emission-computed-tomography myocardial perfusion imaging (MPI) including interference from excessive subdiaphragmatic activity. Our aim was to determine associations between clinical parameters and MPI interference including any potential correlation between interference severity and stomach volume.

Methods and results. Two hundred men and women fasted two hours prior to standard clinical ^{82}Rb myocardial perfusion rest/stress PET. Images were analyzed for radiotracer interference between left ventricle myocardium and extracardiac activity. Furthermore, volume of the stomach was measured. Interference, predominantly caused by ^{82}Rb activity in the stomach, was less severe in stress PET compared to rest (absent in 46% vs 31% of patients during stress and rest, $P < 0.05$). In addition, a large stomach volume was associated with more severe interference in rest ($P < 0.05$) while a high body mass index was associated with less interference.

Conclusion. Among clinical parameters associated with patient size, BMI was the strongest predictor of MPI interference. Furthermore, a large stomach volume was associated with more severe MPI interference, suggesting that sufficient fasting prior to imminent ^{82}Rb PET may be important to reduce interference from adjacent radiotracer activity and consequently improve interpretation of MPI results, especially in small patients. (J Nucl Cardiol 2019;26:1934–42.)

Key Words: Myocardial perfusion • rubidium • cardiac positron-emission-tomography • interference • ^{82}Rb -PET • rubidium PET • myocardial perfusion imaging • myocardial blood flow • subdiaphragmatic interference • cardiac imaging

Abbreviations		^{82}Rb	^{82}Rb
IHD	Ischemic heart disease	SPECT	Single-photon emission computed tomography
MBq	Megabecquerel		
MPI	Myocardial perfusion imaging		
PET	Positron-emission-tomography		

See related editorial, pp. 1943–1945

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INTRODUCTION

Cardiac positron emission tomography (PET) is a well-established modality for the diagnosis and risk-stratification of patients assessed for ischemic heart disease (IHD).¹

Due to several practical advantages, ^{82}Rb rubidium chloride (^{82}Rb), a potassium analog, is increasingly used as the radiotracer of choice in myocardial perfusion imaging (MPI).¹ First of all ^{82}Rb -PET is an accurate method to quantify myocardial flow reserve, a functional parameter associated with adverse cardiovascular events and useful in the evaluation of microvascular dysfunction.^{2,3} Furthermore, ^{82}Rb is produced by a $^{82}\text{Sr}/^{82}\text{Rb}$ generator (CardioGen-82®) with a durability of four to five weeks, which is the reason its use is not dependent on an on-site cyclotron.⁴ Additionally, due to its ultra short half-life of 76 seconds, ^{82}Rb administrations can be repeated at shorter intervals than other used MPI-radiotracers, thus shortening the examination time of typical rest-stress MPI examinations.^{1,3,4} Moreover, ^{82}Rb PET results in a lower radiation exposure than single-photon emission computed tomography (SPECT) imaging with exposure estimates 4- to 5-fold lower than $^{99\text{m}}\text{Tc}$ -based SPECT (effective dose 2 to 3.7 mSv).^{5,6}

Despite the obvious advantages of using ^{82}Rb in MPI it is still prone to some of the same imaging artifacts as SPECT MPI including interpretation problems due to interference from excessive subdiaphragmatic activity. In $^{99\text{m}}\text{Tc}$ -based cardiac SPECT prominent activity is frequently present in subdiaphragmatic organs adjacent to the heart.^{7,8} Activity is present in the liver and bowel as a result of hepatobiliary excretion of the radiopharmaceutical and can be present in the stomach due to reflux of radiopharmaceutical into the gastric lumen from the duodenum or because of uptake of free $^{99\text{m}}\text{Tc}$ -pertechnetate by the gastric mucosa. Typically this activity interferes with evaluation of the adjacent inferior wall but in rare cases, in the setting of a hiatal hernia, the lateral wall can be affected. In contrast, in ^{82}Rb -PET activity is frequently present in the stomach and pancreas presumably as a result of its sodium-potassium-ATPase mediated ^{82}Rb uptake. In SPECT MPI, this issue has been addressed in different ways from drinking milk, water, or carbonated water to low-level exercise to prone imaging.^{7,9,10} Furthermore, Technetium-labeled agents, used in SPECT MPI, have the benefit of a longer half-life compared to ^{82}Rb . This means that if excessive subdiaphragmatic activity is found on SPECT MPI, then a repeated scan is possible, in order to clear excessive activity from the liver, stomach, and bowel in the time from the first to the second acquisition, a strategy not feasible in ^{82}Rb -PET due to the short half-life of the ^{82}Rb -tracer. One aggravating factor

in the degree of interference between ^{82}Rb uptake in the left ventricle and uptake in the stomach might be found in the degree of distension of the stomach. On one hand, a small condensed stomach with greater concentration of ^{82}Rb activity might more often cause interference in MPI while on the other hand a large distended stomach might more often be forced up against the posterior wall of the myocardium to cause interference.

The aim of this study was (1) to determine the prevalence of severe interference, potentially complicating MPI interpretation, between radiotracer activity from subdiaphragmatic activity and the left ventricle myocardium in ^{82}Rb PET MPI in men and women (2) to determine which organs were involved, (3) to determine which clinical parameter associated with patient size (height, weight, and body mass index) was the strongest predictor of MPI interference, and (4) to determine potential correlation with stomach volume.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

Two hundred men and women with a vast array of indications to undergo myocardial perfusion imaging from a clinical protocol were consecutively included over a 7 month period. Patients were instructed to fast 2 hours prior to the examination. The only exclusion criteria were a computed tomography (CT) where the stomach volume could not be measured correctly. In total, 15 patients were excluded due to incomplete scan of the stomach ($n = 14$) or poor stomach definition ($n = 1$).

^{82}Rb Rubidium PET Imaging

Rest myocardial perfusion PET-CTs were performed on a Siemens Biograph mCT/PET 128-slice scanner (Siemens Medical Solutions, Knoxville, TN, USA) as 7 minutes dynamic PET myocardial perfusion scans under the administration of 1000 to 1200 MBq ^{82}Rb from a CardioGen-82 Sr-82/Rb-82 generator (Bracco Diagnostics, Inc., Princeton, NJ, USA). A standard clinical protocol was used. An X-ray scout view over the chest was performed for positioning followed by low-dose CT (120 kV; quality reference effective mAs, 11; rotation time, 0.5 seconds; pitch, 1.5; collimation, 16×1.2 mm) for attenuation correction of the rest emission data. ^{82}Rb was intravenously infused with a flow rate of 50 mL/min, and list mode 3D data acquisition was started with the tracer infusion and continued for 7 minutes. Static and ECG-gated images were reconstructed with a 2.5-minute delay to allow ^{82}Rb clearance from the blood pool. Adenosine stress PET scans were performed subsequent to rest scans, as 7 minutes dynamic PET scans under administration of 1000 to 1200 MBq ^{82}Rb . Adenosine was administered as a continuous intravenous infusion of 840 $\mu\text{g}/\text{kg}$ initiated 2.5 minutes before scan-start and infused over 6 minutes. Registration between PET and CT

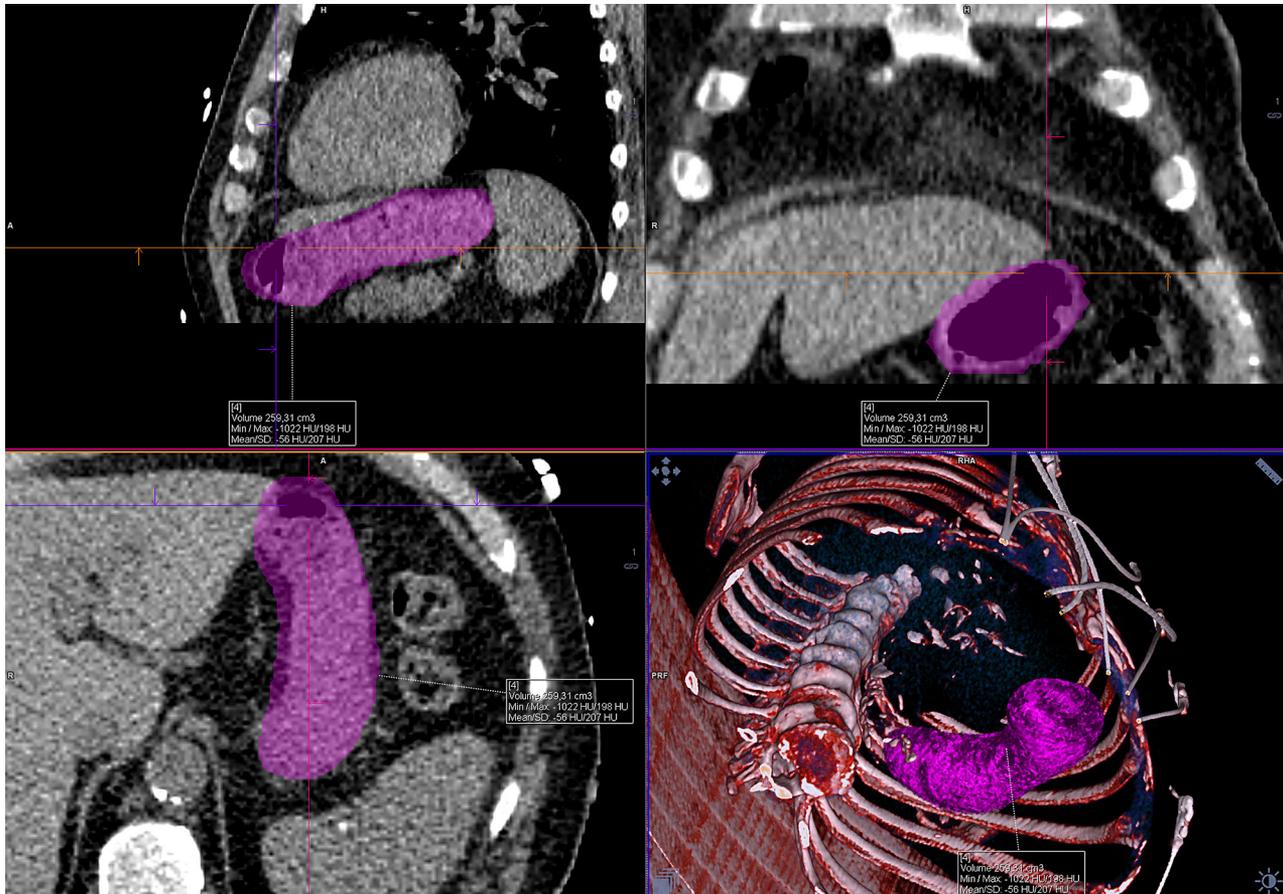


Figure 1. Representation of the stomach in computed tomography shown in transverse, sagittal, coronal, and 3D projection.

images was checked for patient motion, and manual adjustments were made before reconstruction to correct for any minor motion. In cases of significant patient motion between PET and CT, an additional low-dose CT was acquired at the end of the study. Both rest and stress dynamic images used for myocardial blood flow (MBF) quantification were reconstructed into 18 time frames (1×10 , 8×5 , 3×10 , 2×20 , and 4×60 seconds) on a 128×128 matrix, with $2\times$ zoom (voxel dimensions, $3.18 \times 3.18 \times 2.03$ mm) using 3D OSEM reconstruction (two iterations, 21 subsets) with Siemens UltraHD-PET, a 6.5-mm Gaussian postfilter, and attenuation and scatter correction, including prompt gamma-correction.¹¹ PET images were analyzed using Cedars-Sinai Cardiac Suite (Cedars-Sinai Medical Center, Los Angeles, USA) for Syngo.Via (Siemens, Knoxville, USA).

Stomach Volume and Evaluation of Interference

Stomach volume was measured in MM RT Image Suite for Syngo.Via (Siemens, Knoxville, USA) by delineation of the stomach in a number of CT slices and subsequent

interpolation to a 3D contour (Figure 1). The 3D contour was carefully assessed to ensure that it matched the delineation of the stomach and a volume in cm^3 was extracted. An example of a large versus a small stomach volume is shown in Figure 2.

Evaluation of stomach interference was performed according to a method described by Orton et al.¹² In brief, interference severity was classified into four severity groups according to the maximum relative uptake of the region of the overlapping myocardium and stomach. In summary, image intensity was normalized to the maximum myocardial intensity and displayed in a ten-step color scale. Interference was classified as absent (relative intensity ≤ 0.4), mild (relative intensity 0.4 to 0.6), moderate (0.6 to 0.7) and severe (≥ 0.7). For interference to be classified as mild, moderate, or severe it had to have an angular coverage of $\geq 20^\circ$ in ≥ 5 short-axis slices. Examples of interference levels are shown in Figure 3.

Statistical Analysis

Categorical variables were expressed as percentages while continuous variables were reported as means and

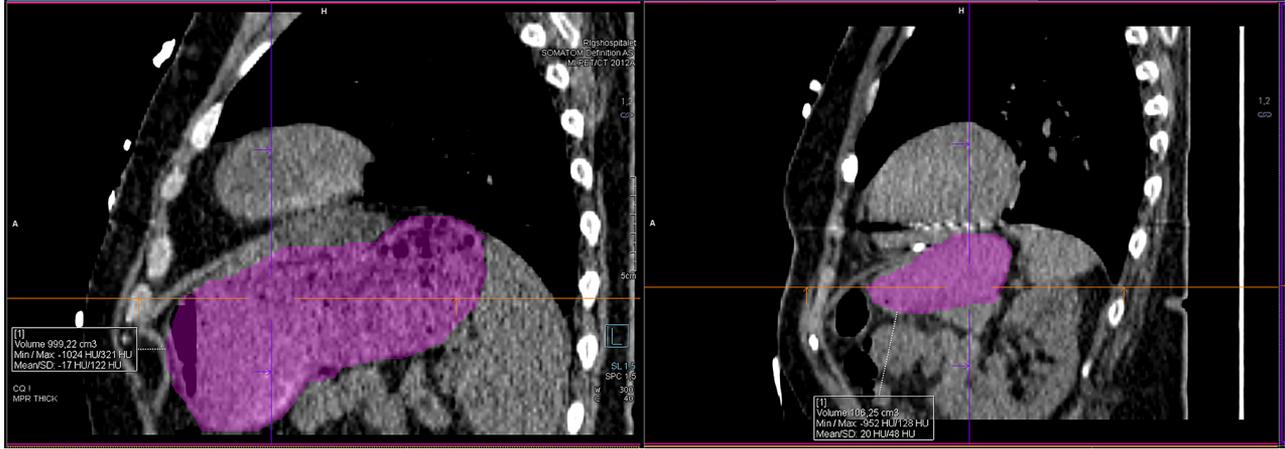


Figure 2. A comparison of a large and a small stomach shown in computed tomography (Left: 999 cm³; Right: 136 cm³).

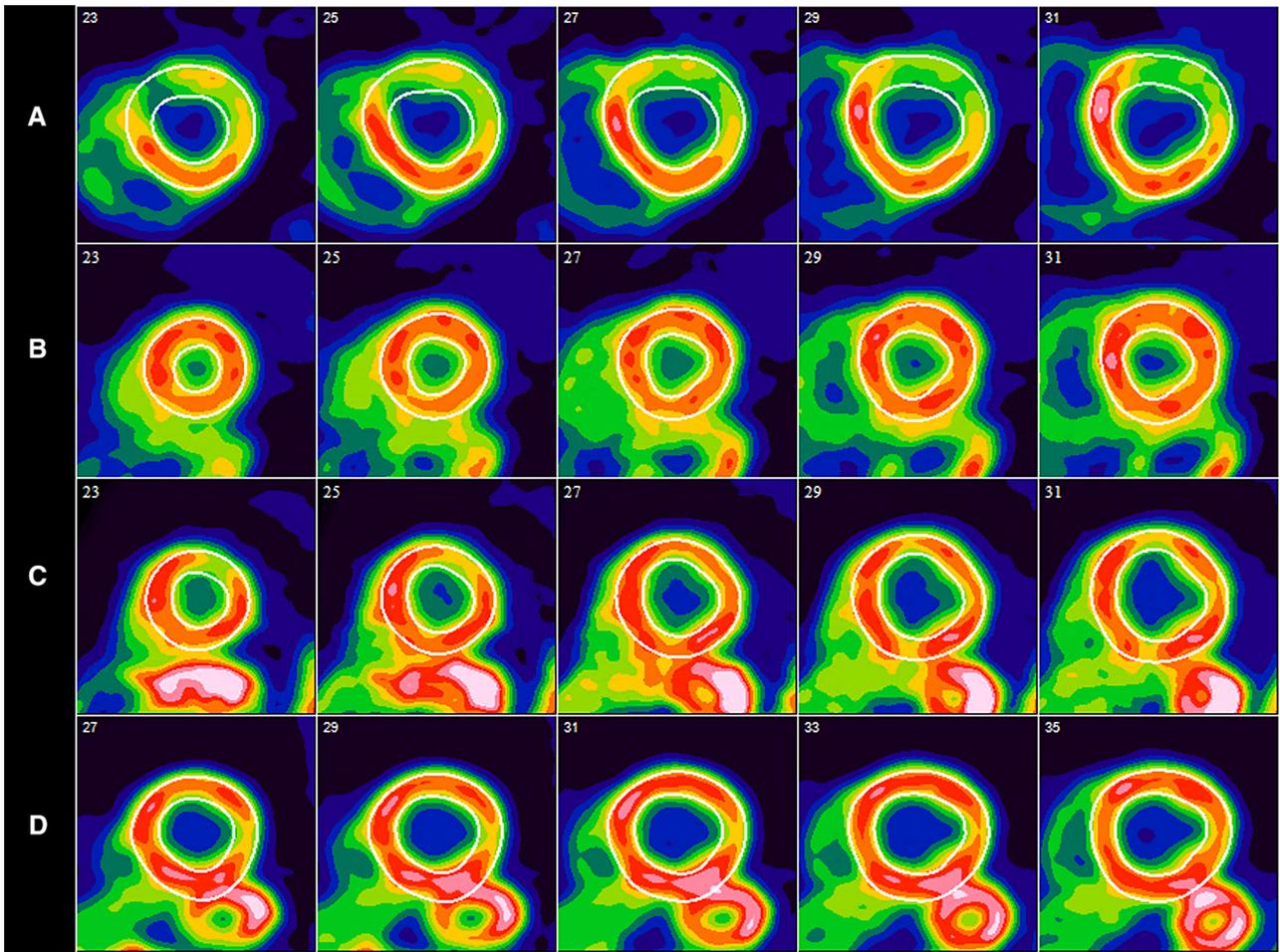


Figure 3. Examples of interference levels shown in splash (A absent, B mild, C moderate, D severe).

Table 1. Baseline characteristics in men and women presented as means (± SD) or number (%)

	Men, (n = 100)	Women, (n = 100)	P value
Age, years (± SD)	63 (± 12)	61 (± 13)	NS
BMI, Kg/m ² (± SD)	27 (± 6)	28 (± 5)	NS
⁸² Rb (rest), MBq (± SD)	1133 (± 164)	1118 (± 161)	NS
⁸² Rb (stress), MBq (± SD)	1129 (± 163)	1112 (± 168)	NS
Previous coronary artery disease, n (%)	30 (30%)	8 (8%)	< 0.0001
Pacemaker/ICD, n (%)	24 (24%)	24 (24%)	NS
Coronary artery bypass graft, n (%)	6 (6%)	1 (1%)	0.05
LVEF (rest), % (± SD)	54 (± 15)	65 (± 15)	< 0.0001
LVEF (stress), % (± SD)	58 (± 16)	69 (± 16)	< 0.0001
Coronary flow reserve, CFR (± SD)	2.33 (± 0.83)	2.35 (± 0.69)	NS
Irreversible myocardial ischemia, n (%)	28 (30%)	10 (11%)	< 0.01
Reversible myocardial ischemia, n (%)	40 (43%)	15 (16%)	< 0.0001
Stomach volume, cm ³ (± SD)	329 (± 179)	215 (± 105)	< 0.0001

BMI, body mass index; MBq, megabecquerel, ICD, implantable cardioverter defibrillator, LVEF, left ventricular ejection fraction

Table 2. Distribution of interference levels under rest and stress

	Rest (n = 199)	Stress (n = 190)	P value
Absent, n (%)	62 (31%)	87 (46%)	< 0.01
Mild, n (%)	91 (46%)	70 (37%)	0.08
Moderate, n (%)	36 (18%)	27 (14%)	0.30
Severe, n (%)	10 (5%)	6 (3%)	0.35

standard deviations. Differences in characteristics between groups were assessed with the chi-square test for discrete variables and students *t* test or one-way ANOVA with test for linear trend for continuous variables in two or more groups, respectively. Logistic regression models were used for multi-variable analyses to determine associations between clinical parameters associated with patient size, such as height, weight, and body mass index (BMI) and ⁸²Rb PET interference. Each of these three models were all adjusted for gender and age. A forest plot was used to illustrate differences in odds ratios between clinical parameters. A two tailed *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using SAS® for Windows, version 9.4 (SAS institute, Cary, North Carolina).

RESULTS

Baseline Characteristics

Baseline characteristics are given in Table 1. Men had a mean age of 63 (± 12) years while women were 61 (± 13) years of age (*P* = non-significant). Men were more likely to have previous ischemic heart disease

compared to women (30% vs 8%, *P* < 0.01). Furthermore, men had significantly lower left ventricular ejection fractions during both rest (54 (± 15)% vs 65 (± 15)%, *P* < 0.0001) and stress MPI (58 (± 16)% vs 69 (± 16)%, *P* < 0.0001) and were more likely to have reversible (43% vs 16%, *P* < 0.01) and/or irreversible (30% vs 11%, *P* < 0.0001) myocardial perfusion defects compared to women. In addition, men had larger stomach volumes than women (329 (± 179) cm³ vs 215 (± 105) cm³, *P* < 0.0001). No difference in BMI between men and women was found (27 (± 6) vs 28 (± 5), *P* = non-significant).

Interference Between ⁸²Rb Activity in the Stomach and Myocardium

Distribution of interference levels between ⁸²Rb activity in the stomach and myocardium during rest and stress MPI are shown in Table 2. No interference was found in 31% to 46% of cases, whereas 3% to 5% of cases were classified as severe interference. As shown,

Table 3. Clinical characteristics according to level of interference between ⁸²Rb uptake in myocardium and stomach

	Interference severity classes											
	Absent		Mild			Moderate			Severe			
	Rest (n = 62)	Stress (n = 87)	Rest (n = 91)	Stress (n = 70)	Rest (n = 36)	Stress (n = 27)	Rest (n = 10)	Stress (n = 6)	P- rest	P- stress		
Age, years (± SD)	63 (± 12)	63 (± 13)	62 (± 13)	61 (± 13)	58 (± 15)	64 (± 10)	68 (± 5)	63 (± 12)	0.37*	0.88*		
Female gender, n (%)	28 (45%)	39 (45%)	48 (52%)	37 (53%)	20 (56%)	13 (48%)	4 (44%)	6 (100%)	0.73	0.07		
Height, cm	173 (± 9)	173 (± 10)	171 (± 9)	171 (± 10)	172 (± 11)	171 (± 9)	173 (± 8)	169 (± 5)	0.65*	0.46*		
Weight, Kg	85 (± 21)	83 (± 21)	77 (± 17)	77 (± 17)	76 (± 16)	78 (± 11)	75 (± 11)	65 (± 15)	0.10*	< 0.05*		
BMI, Kg/ m ²	29 (± 6)	28 (± 6)	27 (± 5)	27 (± 5)	26 (± 4)	27 (± 3)	25 (± 3)	24 (± 5)	0.05*	0.10*		
Rest flow, mg/mL/ min	1.19 (± 0.38)	1.14 (± 0.36)	1.13 (± 0.33)	1.11 (± 0.29)	1.08 (± 0.26)	1.14 (± 0.31)	1.04 (± 0.26)	1.23 (± 0.23)	0.17*	0.47*		
Stress flow, mg/mL/ min	2.44 (± 0.94)	2.46 (± 0.93)	2.58 (± 0.89)	2.60 (± 0.77)	2.74 (± 0.61)	2.61 (± 0.82)	2.21 (± 0.94)	2.75 (± 0.99)	0.56*	0.44*		
CFR (± SD)	2.09 (± 0.61)	2.20 (± 0.67)	2.39 (± 0.75)	2.51 (± 0.83)	2.71 (± 0.86)	2.35 (± 0.74)	2.14 (± 0.78)	2.37 (± 0.96)	0.55*	0.73*		

Table 3. continued

	Interference severity classes								P-stress
	Absent		Mild		Moderate		Severe		
	Rest (n = 62)	Stress (n = 87)	Rest (n = 91)	Stress (n = 70)	Rest (n = 36)	Stress (n = 27)	Rest (n = 10)	Stress (n = 6)	
EF rest (%)	57 (± 16)	58 (± 17)	60 (± 15)	60 (± 13)	62 (± 15)	62 (± 17)	53 (± 23)	61 (± 18)	0.55*
EF stress (%)	61 (± 17)	61 (± 17)	65 (± 15)	65 (± 15)	68 (± 17)	68 (± 18)	56 (± 23)	63 (± 18)	0.47*
Stomach Volume, cm ³ (± SD)	293 (± 183)	285 (± 159)	259 (± 141)	264 (± 144)	239 (± 110)	291 (± 181)	417(± 217)	182 (± 34)	< 0.05*

* P value for linear trend

interference levels were significantly lower during stress MPI compared to rest MPI.

Demographics in different interference levels during rest and stress MPI are given in Table 3. There were no differences in age and gender across interference level classes nor were there differences in rest or stress myocardial blood flows or coronary flow reserves. No association between left ventricular ejection fractions and MPI interference levels during rest or stress was found. Patients with higher BMI tended to have less severe levels of MPI interference (*P* = 0.05 and *P* = 0.10 during rest and stress MPI). Among clinical parameters associated with patient size (height, weight, and BMI), BMI was the strongest predictor of MPI interference during both rest and stress MPI (OR 0.91 (0.85 to 0.96) during rest MPI, *P* < 0.05; OR 0.96 (0.90 to 1.00), *P* = ns) (Figure 4). In addition, a large stomach volume was associated with more severe levels of MPI interference during rest (*P* < 0.05), while this association was not found during stress MPI.

DISCUSSION

This is, as far as we know, the first study to explore the factors of significance for interference between subdiaphragmatic ⁸²Rb activity and the left ventricle myocardium in MPI. The major finding of our study was that (1) in our cohort of patients subdiaphragmal activity interference solely originated from activity in the stomach and not from the pancreas or the kidneys, (2) a large stomach volume was associated with more severe levels of MPI interference, although only in rest MPI. (3) Among clinical parameters associated with patient size (height, weight and body mass index), body mass index was the strongest predictor of MPI interference and tended to be inversely associated. Furthermore, (4) we found no associations between age, gender, rest, or stress blood flows, coronary flow reserves or left ventricular ejection fractions during rest or stress and the level of MPI interference.

In SPECT MPI, where excessive subdiaphragmatic activity is caused by hepatobiliary excretion of the radiopharmaceutical from the liver to the bowel with the possibility of reflux into the gastric lumen or simply by uptake of free ^{99m}Tc-pertechnetate in the gastric mucosa, this has been addressed in different ways.⁷ A study showed that drinking milk after injection might help clear activity from the liver, although there is no consensus.⁹ Others have found a possible beneficial effect by intake of iodinated oral contrast to reduce scatter via absorption of gamma rays emitted from ^{99m}Tc-sestamibi in the bowel¹³ while another study found a benefit in drinking carbonated water prior to SPECT examination.¹⁰ Yet another study found a

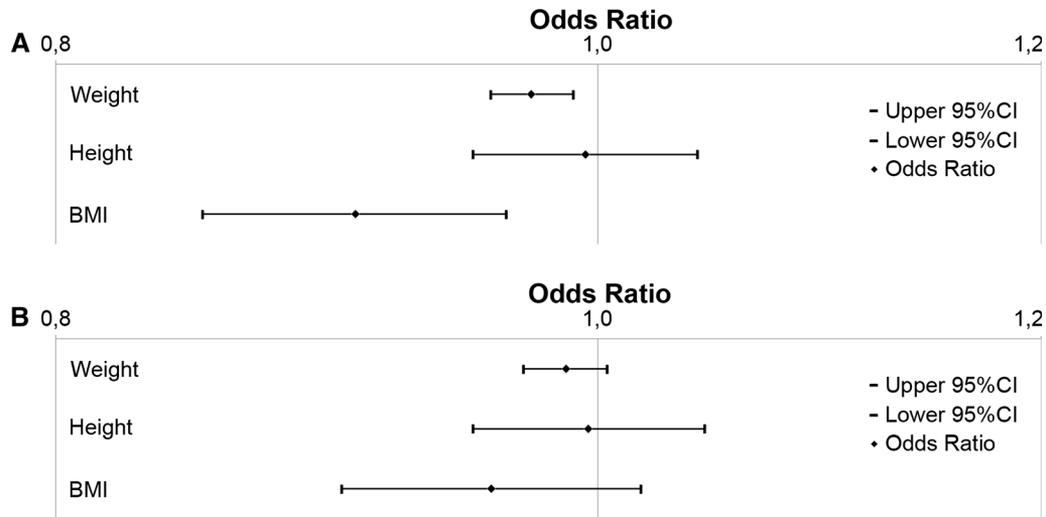


Figure 4. Forest plot showing odds ratios between MPI interference and clinical parameters associated with patient size during (A) ⁸²Rb myocardial perfusion rest PET and (B) ⁸²Rb myocardial perfusion stress PET (each model adjusted for age and gender).

potential preventive effect on bowel activity by the intake of solid food before ^{99m}Tc-tetrofosmin SPECT.¹⁴ The use of pharmaceuticals with potential beneficial effect on scatter from extracardiac activity before ^{99m}Tc-based SPECT has also been examined, among others metoclopramide, that increases gastrointestinal motility, which showed no effect.¹⁵ Among generally accepted approaches to limit subdiaphragmatic activity are intake of water to clear activity from the stomach, prone imaging to help displace subdiaphragmatic organs away from the heart and low-level exercise during pharmacological stress to increase skeletal muscle blood flow thereby reducing splanchnic blood flow and thus subdiaphragmatic activity.^{9,16–20} Furthermore, as previously mentioned, a re-scan within 6 hours after tracer injection is a sound and recommendable approach to address interference from subdiaphragmatic activity accumulation in cardiac technetium SPECT. Due to the very short tracer half-life this is not a valid approach in cardiac ⁸²Rb PET. Nevertheless, the issue with interference from subdiaphragmatic activity has never been addressed in ⁸²Rb MPI and therefore no clinical guidelines to decrease subdiaphragmatic activity interference exist.

Even though, measurement of stomach volume prior to ⁸²Rb-PET in a clinical setting would neither be feasible nor have clinical implications, the association between severity of radiotracer activity interference and stomach volume in ⁸²Rb MPI is important because it may help guide new recommendations for the preparation of patients before imminent ⁸²Rb cardiac PET. The findings of our study, that a large stomach volume was

associated with more severe interference, suggest that sufficient fasting before cardiac PET, thus contributing to a reduction in stomach volume, may be helpful in reducing MPI interference. In addition, fasting might also result in a reduced stomach blood flow which as a consequence may have a synergistic effect, thus reducing MPI interference even more. Furthermore, BMI tended to have an inverse correlation with MPI interference severity, most likely due to a longer distance between stomach and left ventricle myocardium caused by increased amounts of intra-abdominal fat with higher BMI.

High adjacent radiotracer activity will undoubtedly influence MPI results. It is our experience that moderate to severe interference could potentially have an impact on results, constituting 17% to 23% of patients in our study. Due to our definition of interference, a number of ≥ 5 consecutive short-axis slices with interference was required to categorize interference as mild, moderate, or severe. To what extent a small condensed stomach with high ⁸²Rb uptake, which might not yield a high degree of interference due to the definition of severity used, might influence the MPI interpretation remains unknown.

The ultimate goal would obviously be to selectively be able to impair stomach ⁸²Rb uptake during cardiac PET. Even though it may not be possible to completely “turn off” ⁸²Rb activity in the stomach during MPI, it might still be possible to reduce it considerably. Something not highlighted in this study, which gives rise to further consideration, is the potential influence that

different medications may have on MPI interference. Proton pump inhibitors and angiotensin converting enzyme inhibitors for example, may potentially be able to reduce ⁸²Rb uptake, although our own preliminary results in this regard are not yet quite promising.²¹

NEW KNOWLEDGE GAINED

Radiotracer interference with left ventricle myocardium in ⁸²Rb MPI is mainly caused by excessive radiotracer activity in the stomach

Weight and BMI are inversely correlated with MPI interference. Among clinical parameters associated with patient size (height, weight, and BMI), BMI was the strongest predictor of MPI interference.

Patients with larger stomach volumes tended to have higher degree of MPI interference, suggesting a potential benefit from longer fasting prior to examination.

LIMITATIONS

It may be considered a limitation that our study was not exclusively including patients with intermediate risk of ischemic heart disease (IHD) but rather patients with a vast array of indications to undergo cardiac ⁸²Rb PET. On the other hand, there is nothing to suggest that patients with IHD should be any different in this respect compared to other patients undergoing cardiac PET.

CONCLUSION

Among clinical parameters associated with patient size, BMI was the strongest predictor of MPI interference. Furthermore, a large stomach volume was associated with more severe MPI interference. This suggests that sufficient fasting prior to imminent ⁸²Rb PET may be important to reduce interference from adjacent radiotracer activity and consequently improve interpretation of MPI results, especially in small patients.

Disclosure

All the authors declare that they have no conflict of interest.

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